Incense Smoke Exposure: An Appraisal of Organ Toxicity

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Abstract

Background: This narrative type review aimed to address organ toxicity emanating from incense usage.

Methods: An online search using the following MeSH terms "Incense smoke,", "adverse effects," "organotoxicity", "oxidative stress" and "inflammation" was done to identify studies directly applicable to adverse effects of incense smoke exposure.

Findings: Exposure to incense smoke demonstrated various toxicity changes in the kidney, testes, lungs, liver and heart. Renal effects included a decrease in oxidative stress markers GSH and CAT, increase in MDA, serum creatinine uric acid and blood urea nitrogen (BUN). Testicular toxicityrevealed significant disturbances in spermatogenetic patterns, testicular atrophy, germinal aplasia, hypospermia and damage to the basal seminiferous epithelia tissue. In the cardiac muscle, ultrastructural changes, increased oxidative stress, inflammation, and altered cardiac hypertrophic gene expression was noted. Thenegative impact of incense smoke emanating from free radical (ROS), lipid peroxidation and GSH destabilizes vascular homeostasis and initiates ahyperinflammatory response, warranting the need to understand the conceptual basis of the mode of action linked to incense exposure.

Conclusion: We highlight that incense generates ROS which initiates lipid peroxidation through ATP energy depletion and reduction in the natural antioxidants. This subsequently triggers oxidative stress, inflammation and endothelial dysfunction resulting in organotoxicity.

***Keywords**: Heart, incense, liver, lungs, organotoxicity, skin, testes*

Introduction

Incense (from Latin *incendere* "to burn") is composed of aromatic biotic materials and essential oils, which when burned release fragrant smoke [(1)]. The term "incense" refers to the substance itself rather than the odour produced [(2)]. The use of incense dates back to Egyptian antiquity, Babylonians, Indus civilization and the early dynasties of China(Xia, Shang, Zhou and Song).

The presentation of incense is variable in that they may occur as sticks, joss sticks, cones, coils, powders, rope and rocks/charcoal [(3)]. Incense usage differs with regard to culture, custom and the reason for usage

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[4], with many using it for the simple appreciation of its aroma and as a deodorizer/fragrance within their homes [5, 6]. It is used in religious ceremonies for ritual purification, to appease the Gods with its sweet smell and to deter demons[1], in aromatherapy[6], an insect repellant and at funeral ceremonies to mask the smell of decay [7, 8]. In most South East Asian and Middle East countries, domestic incense burning is routine during daily religious rituals [9].

When incense is burnt, it emits smoke that contains CO, CO_2, NO_2 and SO_2, aldehydes, metallic elements, polycyclic aromatic hydrocarbons (PAHs) including benzo(a)pyrene (BaP), naphthalene, fluoranthene and volatile organic compounds (VOCs) such as benzene, toluene and xylene [10-12]. Inhalation of these pollutants in a closed environment are detrimental to human health. In fact, particulate matter from incense burning is 45 mg/g compared a cigarette, which is 10 mg/g [13]. Moreover,incense is associated with a weak mutagenic activity [14].

Nonetheless, despite its widespread availability and access, the mechanism of its adverse effect and toxicity remains a public health challenge[14]. Several studies demonstrate that continuous exposure to incense smoke predisposes the development of asthma, dermatitis, respiratory complications and hypertension[15-17]. Moreover, exposure to carcinogens emitted from incense burning increases the risk of cancer development [18-20]. Furthermore, the pathological and pharmacological effect of incense smoke on organs have been reported in the lung, testis, skin, liver and kidney [19, 21-23].

The adverse effect of incense exposure on different organs is based on short-term and long-term exposure. In fact, long-term exposure to incense smoke increases inflammation of blood vessels thereby influencing blood flow [22]. In light of the negative consequences associated with incense smoke exposure, this narrative type review aimed to address organ toxicity emanating from incense usage.

Pathogenesis of organotoxicity emanating from incense exposure

Although the underlying causal mechanisms of incense exposure remains unclear, changes to oxidative stress, reactive oxygen species (ROS), inflammation, endothelial dysfunction and lipid peroxidation pathways may synergistically and concurrently contribute to pathology.

i. Oxidative stress

Reactive oxygen species are chemically reactive molecules containing oxygen *e.*g., oxygen ions and peroxides. ROS is a natural by-product of the metabolism of oxygen and has an important role in cell signaling and homeostasis [24]. The production of ROS such as peroxides and free radicals lead oxidative stress that causes considerable damage to proteins, lipids and DNA of a cell.

Oxidative stress contributes to NO depletion, emanating from excess superoxide anions generation [25]. Also, the superoxide anions react with NO to produce peroxynitrate. This subsequently oxidizes tetrahydrobiopterin (BH4) [26] which inactivates eNOS thereby exacerbating superoxide anions production [27]. Oxidative stress also upregulates endothelin-1 expression and causes endothelial dysfunction [28].

Oxidative stress activates the specific adaptive stress responseviaan enhanced protein expression of endogenous anti-oxidant enzymes [29]. This stress response protects cells against the reactive oxygen species mediated toxicity whilst maintaining a tissue redox balance [29]. The gene transcription of most anti-oxidant enzymes is regulated via transcription factors, nuclear factor-E2-related factor (Nrf2) and anti-oxidant response elements (ARE) in the genes encoding enzymatic anti-oxidants [30]. Under physiological conditions, Nrf2 is linked to an actin-bound Kelch-like ECH-associated protein 1 (Keap1) that is located within the cytoplasm[31]. However, under the influence of oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it induces the transcription of ARE-regulated genes [30]. Anti-oxidant enzymes such as superoxide dismutase, catalase and glutathione defend the host against the damaging effects

of the free radicals species [30, 32].Several studies have also associated incense exposure to pathophysiological disturbances with increased generation of ROS and/or a depletion of anti-oxidants within the kidney, testes, liver, heart, skin and lungs [33-37].

ii. Inflammation

Inflammation is a natural defense mechanism associated with microbial and viral infection, exposure to allergens, radiation and toxic chemicals, autoimmune, chronic diseases, obesity, alcohol consumption, tobacco use, and a high-calorie diet [38]. Notably, chronic diseases such as cancer, insulin resistance, diabetes mellitus, cardiovascular diseases, atherosclerosis, and aging are associated with an up-regulation of ROS, oxidative stress together with protein oxidation [39, 40].

Inflammation is a major indicator of endothelial dysfunction as endothelial stress is associated with an increased endothelial secretion of chemokines and cytokines [41]. Persistent inflammation may further exacerbate the oxidative stress induced pathology [42]. Oxidative stress is also implicated in vasoconstriction of vascular smooth muscle via upregulation of endothelin-1 expression within endothelial cells, with consequent abnormal vascular function [28]. Thus, oxidative stress is the key force that drives endothelial dysfunction by destabilizing vascular homeostasis via the down-regulation of NO together with an up-regulation of endothelin-1. A strong correlation between incense smoke and oxidative stress was demonstrated by Hussain et al(2019). A significant reversal of oxidative stresswas observed within 30 days of cessation of incense smoke exposure, with consequential up-regulation of endothelial function and inflammation, thus confirming that incense smoke may be responsible for the induction of the pathology[37].

Furthermore, the induction of Cytochromes P450 (CYPs) by BaP or other constituents either alone or in combination in rats exposed to incense smoke, maybe responsible for the mechanistic event for the increase in oxidative stress and inflammation of kidney dysfunction and tissue degeneration [19]. Additionally, myocardial degeneration together with increased oxidative stress and inflammation may contribute to the increased risk of cardiovascular and endothelial dysfunction, as well as irregularity in heart rate amongst incense-smoke exposed subjects [43]. Similarly, rhodinol-based incense generates reactive oxygen species via ROS production that exceeds the body's own natural anti-oxidant defense thereby resulting in oxidative stress and consequent cellular damage [23, 44]. This may explain the decrease in enzymatic and non-enzymatic anti-oxidants such as CAT, SOD, GSH and GPx. Similarly, Ahmed et al., (2013) also reported a decrease in both enzymatic and non-enzymatic anti-oxidants after exposure to incense smoke[34]. Moreover, treatment of human alveolar epithelial cells, A549 with particle matter emanating from incense smoke correlates with increased oxidative stress [45]. Incense smoke combustion is also reported to contribute to reactive oxygen species generation and to increase oxidative stress and induce DNA damage [11].

iii. Lipid peroxidation

Lipid oxidation is a naturally generated process in the body, occurring mainly as an effect of several reactive oxygen species (hydroxyl radical, hydrogen peroxide,*etc*.) or by the action of several phagocytes [46]. Since lipid peroxidation is a self-propagating chain-reaction, the initial oxidation of only a few lipid molecules may lead to significant tissue damage [47]. Lipid peroxidation has been implicated in diseases such as pre-eclampsia and in hepatoxicity, kidney damage, skin damage and testiculotoxicity [34, 48].The mammalian spermatozoon is particularly vulnerable to lipid peroxidation because of the molecular anatomy of its plasma membrane [23]. Unlike somatic cells, mammalian sperm cells have ahighly specific lipidic composition with a high content of polyunsaturated fatty acids (PUFA), plasmolygens and sphingomyelins[23]. Theirunusual plasmalemma content is responsible for its flexibility and the functional ability of sperm cells. The high PUFA content is the main substrate for peroxidation and may provoke severe sperm dysfunction[49, 50]. It is possible that the testicular oxidative status of rats exposed to varying weights of incense (2g and 3g) increases the

action of malondialdehyde(MDA), a product of lipid peroxidation and damages their structure[23, 34]. An earlier study demonstrated that the incense smoke exposure significantly decreased the liver alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) glutathione (GSH) and the activities of SOD, CAT and GPx by significantly up-regulating lipid peroxidation [51].

In light of the above mechanistic actions of incense smoke, physiologic function of various organs may be compromised. These include:

a) Kidney

A significant increase in serum creatinine, uric acid, blood urea nitrogen (BUN), tissue MDA, tumor necrosis factor-alpha (TNF-α) and interleukin-4 (IL-4) levelshave been reported in rats exposed to incense smoke[19]. They also reported a significant decline in tissue glutathione (GSH) and catalase activity together with associated ultrastructural kidney pathology. Furthermore, a significant increase in tissue gene expression of both CYP1A1 and CYP1A2 were noted in incense exposed rats [19]. In Singapore, the long-term daily exposure of the Chinese population to domestic incense burning has been associated with an increased development of end stage renal disease [52].

b) Testes

Rats exposed daily to *Boswelliapapyrifera* and *Boswelliacartetii* - based incense show significant disturbances in sperm kinetics compared to unexposed rats [34]. More specifically, incense smoke causes a secretory dysfunction of Leydig cells with a deficiency in sperm maturation and spermatogenesis [53]. Similarly, over a ten-week period incense burning activates a secretory deficiency in Leydig and Sertoli cells with resultant impairment of epidymal sperm maturation and consequential diminished capacity of spermatozoa to penetrate oocytes [54]. Furthermore, a deregulation of the oxidative pathway is believed to cause a derangement in testicular histology and sperm viability in Wistar rats exposed to rhodinol-based incense [23]. Additionally, a histomorphometric and spermatogenic evaluation of musk-based incense induced testiculotoxicity in adult albino rats with concomitantdecrease in sperm viability, testicular atrophy, germinal aplasia, hypospermatozoa formation and damage to the basal seminiferous epithelial tissue [23].

c) Lung

The continuous exposure to incense smoke initially causes physiological and cellular changes that directly affect the efficiency of respiratory organs especially the lung [55]. Exposure to incense smoke correlates with moderate inflammation and lymphocyte infiltration in lungs of albino rats [56], while other studies have recorded pathology such as lung carcinoma [57]. Alarifi et al., (2004b) reported ultra-structural changes of the alveolar pneumocytes of animals exposed to*bakhour*-based incense[21]. These changes affect the cell organelles and surfactant material of type II cells. Similarly, Alokail et al., (2004) showed that *bakhour* burning adversely affects respiratory health. Moreover, light microscopy evaluation of lung tissue revealed focal emphysema, rupture of alveolar walls, hemorrhage, congestion, edema and peri-bronchial lymphoid cells [36]. In addition, chronic exposure elicits focal necrosis and degradation of epithelial bronchioles together with fibrosis of peribronchial tubes, thickening of alveolar walls and aggregation of lymphoid cells [58].

d) Liver

Using an animal model exposed to Arabian incense smoke a significant decrease in anti-oxidant enzyme activity with concomitant significant elevation in lipid peroxidation; MDA was noted, signifying its hepatotoxic effects [35]. The impact of long-term exposure to incense induces the expression of CYP1A1, CYP1A2, and CYP1B1 mRNAs within the lung and liver [36]. Incense smoke exposure also increases MDA, TNF-α and IL-4 levels with a concurrentreduction of glutathione thereby reducing catalase activity within the liver [36].

e) Heart

Particulate matter generated during incense burning is responsible for variability in heart rate and impaired endothelial function [43]. Importantly, regular exposure to incense is correlated with increased cardiovascular dysfunction [18]. Moreover, ultrastructural changes, increased oxidative stress, inflammation, and altered cardiac hypertrophic gene expression was noted in cardiac muscle exposed to incense smoke [56].

f) Skin

Incense smoke exposure is also associated with dermatological problemssinceit may elevateIgE levels, and cause allergic contact dermatitis [4, 15].An early study observed itchy depigmented macules on the dorsum manus, left shoulder and the abdomen [59]. The same research group also reported cases of contact dermatitis due to long-term exposure to musk *ambrette* vaporized from incense burning [33].

g) Brain

Indoor incense burning is associated with vascular disease to predispose poor cognitive performance related to decreased brain connectivity [60]. An earlier report indicates that incense smoke contains various N-nitroso compounds, which are powerful nervous system carcinogens[61].

1. Figure 1.Conceptual pathway of how incense exposure mediates organ toxicity. Incense generates free radicals (ROS) which initiates lipid peroxidation through ATP energy depletion and reduction in natural body antioxidant such as GSH that triggers oxidative stress, inflammation and endothelial dysfunction resulting in organotoxicity. Moreover, lipid peroxidation is a process generated naturally in small amounts in the body mainly by the effect of several phagocytes. Since lipid peroxidation is a self-propagating chain reaction, the initial oxidation of only a few lipid molecules can lead to significant tissue damage. In addition, oxidative stress can trigger the infiltration of inflammatory mediator which in turn can leads to inflammation of affected tissues. Also, oxidative stress appears to be a key force driving endothelial dysfunction via destabilizing vascular homeostatic by down-regulating NO levels as well as up-regulating endothelin-1 in vascular tissue (developed from Mukhtar et al.,2013; Alokailet al.,2014; Akingbade et al., 2015, Hussain et al., 2016).

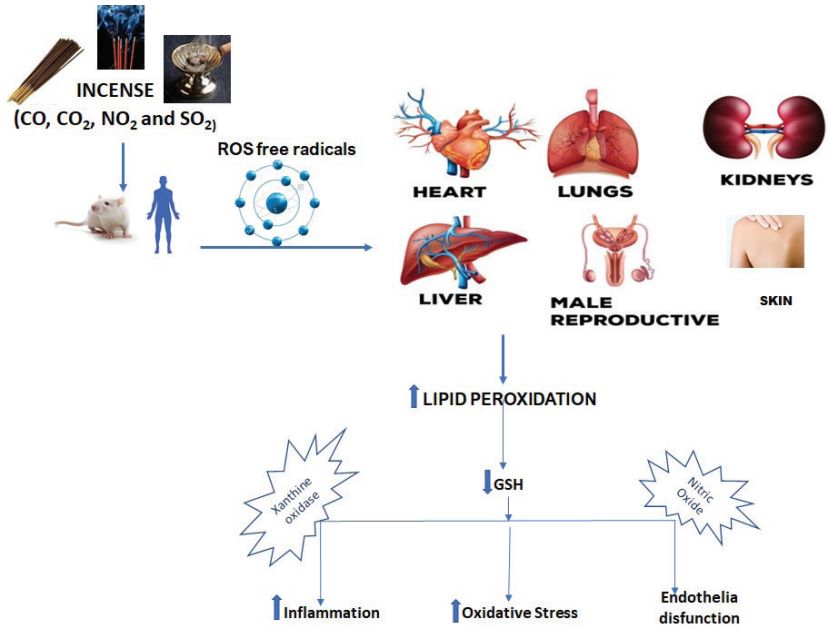

Figure 1. Conceptual pathway of how incense exposure mediates organ toxicity

Conclusions and Recommendation

Incense burning remains an environmental agent of important public health concern, hence it is necessary to understand the conceptual basisof its mode of action. The deleterious capacity of incense smoke inducesphysiological and cellular oxidative stress that emanates from ROS. Consequentially, a decline in lipid peroxidation and GSH destabilizes vascular homeostasis thereby initiating inflammatory elevation of mediators such as MDA, TNF-α and IL-4 levels.Finally, there is an urgent need to create public awareness of the potential side effects of these commonhousehold and religious products.Awareness will lead to a reduction in exposure time and increase ventilation of homes and temples to ameliorate the pathological side effects of incense smoke.

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